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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,422	05/09/2001	Xianxhang Yu	035879-0122	2132

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,422	YU ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-18 and 20-23* is/are rejected.

7)☒ Claim(s) *8 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2004 has been entered.

Please note that the examine assigned to this application has changed.

Claims 1 and 3 have been amended. Claim 23 has been added. Claims 1-23 are pending and under consideration. Acknowledgement is made of applicant election of the species of amoebapore. After review and reconsideration of the subject matter in light of the prior art, the species of melittin will also be examined at this time.

Sections of the text from Title 35, US code not found in this action can be found in a previous Action.

Claims 5, 7, 8, 16, 18, 19, 22 are objected to for lacking sequence compliance. The claims contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), but are not identified by Sequence Identifiers. Appropriate correction is required.

Claims 3-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim recites "analogs thereof" and "derivatives thereof". It is unclear if the "derivatives thereof" is in reference to only the "analogs thereof" or if "derivatives thereof" encompasses derivatives of the individual recited species. Further the metes and bounds of a "analog" and "derivative" in reference to the recited species cannot be determined with exactitude as attributes of an "analog" and "derivative" are not defined by the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

It is noted that the claims are rejected because the specification lack a definition of an "analog" and "derivative". The instant claims are examined to the extent that they read on amoebapore, melittin and magainin and analogs thereof and derivative thereof. Thus, the claims encompass a genus comprising amoebapore, amoebapore analogs and amoebapore derivatives; a genus comprising melittin, melittin analogs and melittin derivatives and magainin, magainin analogs and magainin derivatives, and method reliant upon the identity of the species within all three genuses. Each genus is highly variant because is tolerates species which differ substantially in structure from the parent compounds of amoebapore, melitttin and magainin. The specification provides not limitations which would allow one of skill in the art to determine if a given protein was indeed a member of the claimed genus, because the structural requirements for membership within the genus are not defined by the specification or set forth as a claim limitation. The specification does not provide examples of a representative number of species which fall within the bounds of each of the genuses. Thus, the disclosure of amoebapore, melittin and magainin does not sufficiently describe the claimed genus, because the genus encompasses members which differ substantially in structure from the parent compounds. One of skill in the art would reasonably conclude that applicant was not in possession of the genuses of amoebapore, amoebapore analogs and amoebapore derivatives, melittin, melittin analogs and melittin derivatives, or magainin, magainin analogs and magainin derivatives. It logically

follows that method claims reliant upon the identify of a genus of products which are not adequately described, cannot be adequately described.

Claims 1-3, 6-7, 9-14, 17, 18 and 20 are rejected under 35 USC 103(a) as being unpatentable over Pinto et al (The Prostate Journal, Feb 1999, Vol. 1, pp. 15-26, cited in a previous Office action) in view of Julian et al (US 5,717,064).

Claim 1 is drawn to a procytotoxin comprising a peptide having at least one lysine residue bound via a peptide bond to at least one amino acid via the e-amino group of said lysine residue acts to prevent the peptide from forming a lytically active conformation. Claim 2 embodies the procytotoxin of claim 1 wherein the cytotoxic peptide is a pore-forming cytolytic peptide. Claim 3 embodies the procytotoxin of claim 2 wherein the cytolytic peptide is selected from the group consisting of amoebapore, melittin and analogs thereof and derivatives thereof.

Pinto et al teach that PSMA can be used as a target for prodrug activation because PSMA is strongly expressed in prostate cancer cells, particularly in metastatic tumor and it can be upregulated by androgen deprivation. Pinto et al teach that other positive features which recommend PSMA as a target for prodrug activation is that it is strongly expressed in the vascular endothelium of tumors but not in the vascular endothelium of normal tissues. Pinto et al teach that strategies which employ intravenous administration of poly-g-glutamated drugs is a promising approach that would maximize toxicity to cells expressing PSMA and would minimize the toxicity of the drugs at other sites (page 22, column 1, bridging paragraph to column 2). Pinto et al teach that PSMA is active against both g and a terminal Glu residues (page 20, first column, lines 22-30). Pinto et al teach polyglutamated drugs but do not specifically teach lytic peptides as drugs..

Julian et al teach naturally occurring lytic peptides including an overall basic charge, and the ability to form amphipathic a-helices (column 1, lines 20-23). Julian et al teach that melittin and magainin are included in these lytic peptides (column 1, lines 23-27). Julian et al teach that lytic peptides show toxicity to transformed cells relative to normal cells because transformed cells have cytoskeletal deficiencies relative to normal cells (column 2, lines 1-9). Julian et al teach that lytic peptides can act as agents of cell proliferation in some normal cell types (column 2, lines 10-22). Julian et al teach that each lysine side chain contains an e-amino group which

provides the peptide with a unit positive charge at physiological pH and that the combined charges from multiple lysines side chains contribute to the polarity and thus the regional hydrophilicity required for the amphipathic a-helix. Julian et al teach that amphipathy alone does not provide for lytic action and it is necessary to have an overall positive charge density for lytic activity. Julian et al teach modification of the e-amino groups by methylation which decreases the susceptibility of the peptide to tryptic hydrolysis but maintains the lytic activity of the peptide since the overall charge density is not altered by methylation (column 6, lines 15-28).

It would have been prima facie obvious a the time the claimed invention was made to modify the e-amino groups of melittin or magainins by adding Glu residues. One of skill in the art would have been motivated to do so by the suggestion of Pinto et al that PSMA be targeted as a pro-drug activating enzymes due to its ability to remove terminal g and a Glu moieties. One of skill in the art would recognize that the presence of the Glu moiety on the lysines of melittin or magainin would neutralize the overall positive charge density because Glu residues carry a negative charge. One of skill in the art would be motivated to temporarily neutralize the overall positive charge of the lytic peptides in order that said lytic peptides would not exert a proliferative or toxic effect on normal cells. One of skill in the art would understand that when in the vicinity of prostate cancer cells expressing PSMA, the g and a terminal Glu residues would be removed due to the carboxypeptidase action of PSMA and thus the positive charge density will be restored to the lytic peptide. further, it would be inherent in the reaction of the lytic peptides with Glu that said lytic peptides would comprise lysine residues, each of which were modified by the Glu reagent and would thus comprise the peptides of claim 7 and 18 since the claim language reads on a procytotoxin "having" the recited peptide structure which is synonymous with "comprising" said recited structures.

Claims 1-7, 9-18 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinto et al (The Prostate Journal, Feb 1999, Vol. 1, pp. 15-26, cited in a previous Office action) and Julian et al (US 5,717,064). as applied to claims 1-3, 6-7, 9-14, 17, 18 and 20 above, and further in view of Leippe et al (PNAS, 1994, Vol. 91, pp. 2602-2606, cited in a previous Office action).

Claim 4 embodies the procytotoxin of claim 2 wherein the cytolytic peptide is selected from the group consisting of ameobapores, amoebapore analogs and amoebapore derivatives. Claim 5 embodies the procytotoxin of claim 5 having the recited peptide structured. Claim 1`5 embodies the method of claim 14 wherein the cytolytic peptide is selected from the group consisting of ameobapores, amoebapore analogs and amoebapore derivatives. Claim 16 embodies the method of claim 14 wherein the procytotoxin has the recited structures. Claim 21 embodies the procytotoxin of claim 2 wherein the cytolytic peptide is an amoebapore. The combination of Pinto et al and Julian et al render obvious the instant claims for lytic peptides which are melittin and magainin. Neither Pinto et al nor Julian et al teach amoebapore as a lytic peptide.

Leippe et al teach amoebapore as a cytolytic pore forming peptide (page 2606, column 1, second paragraph). Leippe et al teach that a-helices are the preferred structural entities of pore-forming peptides and proteins (page 2605, first column, lines 5-6) and that positively charged residues are crucial for the activity of amoebapore (page 2603, second column, lines 2-3), thus corroborating the teachings of Julian et la regarding the positive charge density on the amphipathic helix. Leippe et al teach that melittin had a relative cytolytic activity of 40% that of full length amoebapore (page 2604, Table 1). Julian et al teach that previous studies have indicated that replacement of amino acid residues within a helix may be carried out without substantial loss of activity as long as the segregation of polar and apolar residues on opposing faces of the helix us preserved (page 2605, second column, lines 9-13) thus fulfilling the specific embodiments of analogs and derivatives of melittin, magainin and amoebapore..

It would have been prima facie obvious at the time the claimed invention was made to substitute amoebapore for melittin in the method of treating prostate cancer rendered obvious by Pinto et al and Julian et al. One of skill in the art would have been motivated to do so by the teachings of Leippe et al on the properties of amoebapore versus melittin. One of skill in the art would be motivated to do so because amoebapore exhibits more cytolytic activity per picomole as melittin. One of skill in the art would be motivate to provide a procytotoxic peptide having more lytic activity per picomole when unmasked by PSMA in the vicinity of prostate tumor cells and endothelium expressing PSMA. One of skill in the art would also understand that amino acid substitution on lytic peptides comprising a-helices can be carried out as long as the

segregation of polar and apolar residues are maintained and as long as the lytic peptide in its "unmasked form" has a net overall positive charge density on the polar side of the helix.

Applicant argues that there would be no motivation, based on the teachings of Pinto et al to render obvious the instant invention because Pinto et al teaches that Glu residues are sequential removed from Methotrexate, which is not rendered non-toxic by the presence of the Glu residues. Applicant maintains that the Glu residues act to prevent the uptake of the Methotrexate rather then to neutralize the cytotoxic activity of the drug and therefore one of skill in the art would not be motivated to add Glu residues to the lytic peptide of the instant invention. This has been considered but not found persuasive. Pinto et al suggest the use of Glu-conjugated drugs in a broader sense which is not confined to methotrexate. Further, the mechanism with which toxicity is blocked by the Glu residues is not important in the broad teaching of pro-drug strategies. If methotrexate is prohibited from cellular entry due to the presence of the Glu residues, the presence of the Glu residues provides a pro-drug strategy and the drug must be internalized before it can be effective. The argument that the drug toxicity itself is not impeded by the presence of the Glu residues is irrelevant because of the drug cannot be taken up in sufficient quantities it will not be able to exert cytotoxicity.

Claims 8 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/9/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER